

Nutritional Influences on Age-Related Frailty

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Abstract

Frailty and malnutrition are both highly prevalent in the older populations. Frailty has multifactorial origin, and is regarded as a fundamental risk factor for deteriorating health status and disability in elder people. It is estimated that prevalence rates for frailty and pre-frail reach as high as 27% and 51%, respectively. The nutritional deficiency is a key to the development of frailty, and interventions focused on the nutrition can prevent the transition of frailty into disability. The critical role of micronutrients in this context suggests the need to improve the quality of food eaten by elder people, not just the quantity. This review aims at summarizing the recent literature on the nutritional links to frailty, frailty components and frailty-related parameters such as low muscle strength and low walking speed, and implications for strategies to prevent or delay frailty in older age.

Keywords: Frailty; Nutrition; Malnutrition; Functionality; Elderly; Micronutrients; Antioxidants

Introduction

Over the past century, the world has enormous changes, including a historically unprecedented decline in mortality and increase in population growth. It will see a new set of demographic challenges such as the subsequent aging of populations in both developing and developed countries. The 20th century was the century of population growth, but the 21st century will go into the history books as the century of aging [1]. Then the rise in morbidity of the aging population will increase the medical costs and the burden on national healthcare systems. Therefore, a complementary approach to improve the health of older people would focus on appropriate interventions from a much earlier age in order to prevent frailty, which is described as a syndrome that is marked by loss of function, strength, physiologic reserve, with increased vulnerability to morbidity and mortality. Recently, expert panels have suggested that the operational definition of frailty include strength, balance, nutrition, endurance, mobility, activity, cognition, and psychological measures [2]. The main interest in the concept of frailty is related to its reversible nature, and interventions focused on the determinant factors of frailty can prevent the transition of frailty into disability [3].

Many epidemiologic studies of frailty have been performed, using a variety of frailty measures. Using the most commonly applied frailty measure, initially validated in the Cardiovascular Health Study population, one study showed that approximately 7% of the community-dwelling population was frail, 44% intermediate, and 46% non-frail [4]. The prevalence of frailty was even higher in the Women's Health and Aging population, with up to 11.3% of this population meeting frailty criteria from another study [5]. A recent publication implementing Fried's criteria identified prevalence rates in various

European countries ranging from 6% to 27% for frailty and from 35% to 51% for pre-frailty in persons above age 65 [6].

Frailty can be triggered by multiple pathophysiological processes such as malnutrition, hormone imbalance, chronic inflammation, immune deficiency, sarcopenia, and multimorbidity. An overview on the influencing factors on frailty or frailty-related parameters including the age [7,8] gender [1,9] malnutrition [4,10-13], comorbidity [14,15], hormonal imbalance, cytokines, oxidative stress, body composition changes, neuropsychological disorders, and socio-economic factors. Frailty often leads to deterioration of health status, immobilization, disability and death; it is particularly characterized by a reduced functional reserve and increased vulnerability to internal and external stressors [16]. Hence recognition and treatment of the cause for frailty and the frailty syndrome itself represent a key approach to improve the care for older people, particularly as frailty is highly prevalent in this population [17,18]. This review aims at summarizing the recent literature on the nutritional links to frailty, frailty components and frailty-related parameters such as low muscle strength and low walking speed, and implications for strategies to prevent or delay frailty in older age.

Malnutrition in Older People

Malnutrition of both macro- and micronutrients has been identified as an important risk factor for the development and severity progression of frailty in older people [19]. Older persons are at risk for "malnutrition" due to decrements in metabolic rate, lean body mass, gastrointestinal function, sensory perception, and fluid and/or electrolyte homeostasis. Poor oral health, chronic disease, polypharmacy, social isolation, hospitalization, cognitive impairment, and pain are contributory. The ability to consume, digest, absorb, utilize, traffic, and excrete is central to nutritional adequacy and ultimately to overall nutrition. Nutritional adequacy becomes a "chicken or egg" dilemma, as frailty imposes decrements in adequacy,

and malnutrition contribute to frailty's development [20,21]. Malnutrition speeds lean body mass loss and decreases competence and therefore underlies declining grip strength, gait speed, and physical function in the frail older adult [22].

In comparison with younger ages, older adults eat more slowly, they are less hungry and thirsty, consume smaller meals, and they snack less [23]. Although food intake declines with aging which is possibly due to lower caloric requirements to maintain reduced lean body mass, inadequately low nutritional intake is frequently observed among older people, especially in those with increased care needs [24]. The mechanisms for the "anorexia of aging" are not fully understood but there may be arrangement of physiological, psychological, and social factors that influence appetite and food consumption, including loss of taste and olfaction, increased sensitivity of the satiating effects of meals, chewing difficulties, and impaired gut function [23,25]. The negative consequences of these changes are compounded by the effects of functional impairments that impact on the ability to access and prepare food, psychological problems such as depression and dementia, as well as the social effects of living and eating alone. Low food intakes and monotonous diets put older people at risk of having inadequate nutrient intakes [26]. Thus in a vicious cycle, declining muscle strength and physical capability in older age may increase the risk of poor nutrition, whilst poor nutrition may contribute to further declines in physical capability.

The U. S. National Health and Nutrition Examination Survey (NHANES III) identified low energy and nutrient intake in up to 21% of the free-living older study population [27]. The InCHIANTI study (In-vecchiare in Chianti/Aging in the Chianti area, Italy) which examined nutritional status and nutritional intake in the general population including old and very old people, found a strong age-dependency of low energy, protein and micronutrient intake [26]. Especially people older than 85 years had the lowest dietary intake of any examined nutrient which was in many cases below official recommendation. Twenty nine percent of women and 38% of men in this age group did not meet their recommended protein intake. This proportion was even higher for some vitamins and trace elements. The National Diet and Nutrition Survey in the UK, 14% of older men and women living in the community, and 21% of those living in institutions, were at medium or high risk of under-nutrition [28].

Recent studies on nursing home residents found an even higher prevalence of poor nutrient intake. Inadequate energy intake was identified in 60% of the examined population, and inadequate micronutrient intake of vitamin E, vitamin B6, folate, magnesium and Zinc in 70% [29,30]. Similar findings were obtained when screening tools suitable for the older population such as the mini nutritional assessment (MNA) were applied in the nursing home setting. Kulnik et al. found that 38% of nursing home residents were malnourished, while another 48% were assessed as "at risk" of malnutrition. Estimates of the prevalence of under-nutrition in older patients admitted to hospital are even greater, ranging up to 72% [31,32]. A recent study from UK revealed inadequate food consumption, defined as having eaten less than three-quarters of the served dishes, in 67% of geriatric acute care patients [33]. These figures are clearly substantial and indicate that there are significant numbers of older adults living in developed settings who currently have less than optimal nutrition.

Association of Inadequate Nutritional Intake with Frailty

There are two consequences declining food intakes in older age that could be important for muscle mass and strength deficient which result in frailty [23]. Firstly, lower energy intakes, if not matched by lower levels energy expenditure, lead to weight loss, including a loss of muscle mass. Secondly, as older people consume smaller amounts of food, it may become more challenging for them to meet their nutrient needs—particularly for micronutrients. For older people with low food intakes, this highlights the importance of having diets of adequate quality. Bartali et al. established a link between deficient nutritional intake and the frailty syndrome based on InCHIANTI study data implementing Fried's criteria [19]. Twenty percent of the InCHIANTI population was frail and out of those who were frail more than 53% showed deficient intake of at least one out of nine examined nutrients.

An energy intake of less than 21 kcal/kg body weight/day was strongly associated with being frail [34]. This observation was also valid for some micronutrients even independently from energy intake. Based on data from the Women's Health and Aging Study (WHAS), Semba et al. identified low serum micronutrient concentrations as frailty predictors [7], in which he estimated that each additional nutrient deficiency raised the risk of frailty in older woman by almost 10%. At baseline, one third of the study participants were frail with significantly lower serum concentrations of numerous micronutrients as compared to their non-frail peers. In the course of regular follow-up examinations about one third of the non-frail study participants become frail.

Thus, as exemplified by the two mentioned studies, inadequate intake of energy and low serum concentrations of micronutrients have been associated with an increased prevalence of frailty and an increased risk of becoming frail in the future. The nutrients that have been mostly consistently linked to sarcopenia and frailty in older adults are vitamin D, protein, and a number of antioxidants, that include carotenoids, selenium, and vitamins E and C [34]. This emphasizes the importance of the quality of diets of older adults, as well as the quantity of food consumed, to ensure that intakes of a range of nutrients are sufficient.

Nutritional Diet Modifiable Influence on Age-Related Frailty

Protein

A number of studies have pointed to protein as a key nutrient in the elderly [35]. Protein intake greater than the amount required to avoid negative nitrogen balance can ameliorate chronic wasting (i.e., rapid loss of muscle mass) associated with the aging process [36]. And other physiological process can also potentially benefit from increased protein intake. Examples include improved bone health [37], maintenance of energy balance [38], cardiovascular function [39,40] and wound healing [41]. Benefits of increased protein intake may be reflected on not only improved function and quality of life in the healthy elderly, but also the ability of hospitalized elderly patients to recover from disease and trauma. Hence health outcomes are improved and cost of care is decreased [42] because over 40% of hospital admissions occur in individuals 65 years and older. The average length of hospitalized stay of patients 65 years and older is 2 days longer than younger age groups [43] due in part to a loss of functional capacity related to depleted muscle mass.

Physiological changes that occur with aging include a loss of muscle mass that is not dependent on disease [44]. Continuing loss of muscle mass eventually leads to sarcopenia which has been termed “nutritional frailty” to clarify the close interrelationship between poor nutritional status, loss of muscle mass and muscle strength, and functional decline [45]. The importance in addressing sarcopenia is clear in light of its correlation to functional impairment [46,47], disability [48,49], falls [50], frailty [51], and the loss of independence that increases with aging [52]. Many elderly patients are institutionalized prior to hospitalization, and as 85% of institutionalized patients are classified as malnourished. One-half of this number is protein under-nourished [53-55]. Once in the hospital, post-surgical or stress inflammation coupled with physical inactivity and inadequate protein-energy intake results in further loss of muscle mass that delays recovery in the elderly, all of which contribute to higher readmission rates following discharge [56,57].

Risk for protein energy malnutrition has been reported as high as 15% of community dwellers and 65% hospitalized and 75% institutionalized frail older adults [34,58,59]. In community-dwelling older people examined by the US Health, Aging and Body Composition Study (Health-ABC), Houston and colleagues demonstrated that low dietary protein intake was associated with loss of lean body mass (i.e. muscle mass) as measured by dual energy X-ray absorptiometry (DEXA) [60]. All participants in the Health-ABC study lost of muscle mass during the three year follow-up period, but those with lowest protein intake at baseline (0.7 g/kg body weight/day) lost more than 40% more muscle mass than those with highest protein intake (1.1 g/kg body weight/day). It was furthermore demonstrated that lower serum albumin concentrations, even within the normal ranges, was associated with greater loss of muscle mass in a five-year follow-up [61].

Known and colleagues examined serum albumin and vitamin D, which are physiologically interconnected in muscle of function and metabolism, and their association with physical performance among community-dwelling older Japanese [62,63]. Study participants with isolated deficiencies of either albumin or vitamin D had poor muscle strength as assessed by knee-extension power and hand-grip strength (one of Fried’s criteria) and impaired balance capability as assessed by the time up-and-go test and functional reach. Even worse functionality, though, was found in persons with deficient serum concentrations both albumin and Vitamin D. These findings should be interpreted considering the growing evidence that older people hospitalized for acute disease may require a higher protein intake to maintain a positive nitrogen balance than previously assumed and officially recommended in healthy older people [64].

Dietary protein provides amino acids that are needed for the synthesis of muscle protein, and importantly, absorbed amino acids have a stimulatory effect on muscle protein synthesis after feeding [65]. In the Women’s Health Initiative Observational Study significant indicated that protein, corrected for energy, was related in a dose-responsive manner to decreased risk for frailty, so that a 20% increase resulted in a 32% lower risk [66]. This translates into high bioavailable protein levels of 1.5 g/kg body weight or 20% of total calories being protective. In a randomized controlled trial of 41 subjects with sarcopenia, oral essential amino acid mixture increased body weight, decreased insulin resistance, decrease TNF- α , and increased IGF-1 and lean body mass without negatively influencing renal function [67]. The dietary protein requirement for an elderly individual is dependent on their health status. An intake of the Recommended Dietary Allowance

(RDA) of 0.8 g protein/kg/day is inadequate to maintain lean body mass in the average healthy elderly individual [68]. Evidence indicates that protein intake greater than the RDA can improve muscle mass, strength and function in elderly. It appears that an intake of 1.5 g protein/kg/day, or about 15% to 20% of total caloric intake, is a reasonable target for elderly individuals wishing to optimize protein intake in terms of health and function (optimal protein intake).

Fatty acid

There are some observational evidences to support an effect of n-3 long-chain polyunsaturated fatty acids (LCPUFA) status on muscle function, as higher grip strength was found in older men and women who had greater consumption of oily fish, one of the richest sources of n-3 LCPUFAs in the UK diet [69]. In a recent randomized controlled trial, supplementation of older adults with n-3 LCPUFA (eicosapentaenoic and docosahexaenoic acids) resulted in an enhanced anabolic response to amino acid and insulin infusion. Whilst these novel data suggest that the stimulation of muscle protein synthesis by n-3 LCPUFA supplementation could be useful for the prevention and treatment of sarcopenia [70]. “Healthy” diets, characterized by greater fruit and vegetable consumptions, whole-meal cereals, and oily fish, have been shown to be associated with greater muscle strength in older adults [69]. Benefits of healthier diets and greater fruit and vegetable consumption on physical function in mid-life have also been described in women in the Whitehall study [71], and in men and women in the Atherosclerosis Risk in Communities Study [72]. Intervention studies that take a food-based of “whole diet” approach are likely to change intakes of a range of nutrients and, therefore, have the potential to be more effective than single nutrient supplementation studies in preventing age-related losses in muscle mass and strength.

As a result of the high risk rates for malnutrition, improving energy and overall nutrient intake has been investigated in a variety of settings using a number of different strategies such as supplements, Meals on Wheels, flavor augmentation, assisted feeding, and meal-time environment enhancements [73-75]. Use of supplements has been shown to reduce mortality by as much as 34% in malnourished frail persons whose energy requirements are estimated as (20-30) kcal/kg body weight/day [76-78]. Several studies have noted an increase in total energy intake and weight gain, without corresponding increases in lean body mass or muscle strength indices, after supplementation with a nutrient-dense, high energy nutritional drink [79-80]. In a randomized controlled study of a high calorie, micronutrient enriched supplement, a significant increase in immune competence and biochemical markers of antioxidant capacity was reserved after 6 months [81,82]. Caloric supplements produce a small weight gain and may reduce mortality in undernourished older people. However, a recent Cochrane collaboration reported no evidence of improvement in functional parameters with caloric supplements overall, but there may be a beneficial effect on mortality in people who are undernourished [83].

Micronutrients

“Oxidative stress” caused by free radicals is considered a major damaging influence on macromolecules (enzyme, lipids, DNA), a contributor to aging at the cellular level and an influencing factor on disability and mortality in older people [84-89]. An accumulation of free radicals may lead to oxidative damage and contribute to losses of muscle mass and strength [65]. The action of free radicals are normally counterbalanced by antioxidant defense mechanisms that include the

enzymes superoxide dismutase and glutathione peroxidase, as well exogenous antioxidants derived from the diet, such as selenium, carotenoids, tocopherols, flavonoids, and other plant polyphenols [65,90].

Carotenoids constitute a group of antioxidants and comprise vitamin precursors and vitamin-like molecules, such as carotene, lycopene, lutein and several more which are utmost importance to scavenging free radicals [89]. The main food source for carotenoids is in fresh fruits and vegetables. Carotenoid serum concentrations are regarded the most valid markers of such intake [90]. On InCHIANTI study, higher plasma carotenoid concentrations were associated with a lower risk of developing a severe walking disability over a follow-up period of 6 years; after taking account of confounders that include level of physical activity and other morbidity, the odds ratio was 0.44 (95% CI 0.27-0.74). Low vitamin D (OR=2.4, CI=1.5-3.7, $p<0.001$), E (OR=2.1, CI=1.3-3.3, $p<0.003$), C (OR=2.2, CI=1.3-3.5, $p<0.001$), and folate (OR=1.8, CI=1.2-3.0, $p<0.01$) [91] were associated with frailty. Similarly in the Women's Health and Aging Studies, highly significant associations were found between frailty risk and vitamin D, the carotenoids, the B vitamins, calcium, zinc, and selenium [19]. Mechanistically, these nutrients play an important role in inflammation, quenching free radicals, neuromuscular function, systemic homeostasis, and bone health.

Many vitamins have antioxidative capacity, e.g. the vitamin A (retinol), C (ascorbate), D (cholecalciferol) and E (tocopherol group). Low serum levels vitamins and minerals such as fat soluble vitamin A, D, and E; water soluble vitamin, such as B6, B12, folate, and C; and minerals such as calcium, zinc and selenium have been independently associated with frail indicators [91]. Vitamin D supplementation is effective for fall prevention and improving balance. In one report, lower serum levels of 25-hydroxyvitamin D (<20.0 ng/mL) were associated with a higher prevalence of frailty at baseline in a group of 1600 men over age 65, but did not predict greater risk for developing frailty at 4.6 years [92]. In an analysis of NHANES data, low serum levels of vitamin D, defined as less than 15 ng/mL were associated with a 3.7 fold increased risk of frailty, after adjustment for all confounders [93]. Vitamin D influences calcium absorption, retention, utilization, and trafficking. Advanced ages, along with high levels of phosphorus, phytates, and dietary acid load, among other factors, decrease absorption, while the requirements for the mineral increase. Levels of vitamin D are generally low in frailty, while other factors that diminish calcium absorption are higher, leading to poor bone health and furthering disability. This particularly dangerous in the older, sarcopenic obese population, where there are pronounced decreases in mobility and no benefit is derived from the extra shear force of body weight on bone [94,95].

Some trace elements, too, like selenium bear antioxidative capacity after integration into proteins (selenoenzymes) where selenium constitutes the active center. Zinc, is involved in immune function and wound healing which are highly relevant attributes particularly at an advanced age [96]. In a randomized control trial, zinc was administered along with essential amino acids to frail older adults and was significantly associated with decreased bone resorption indices, increased IGF-1 responsivity and better overall physical functioning [97]. Subclinical B12 deficiency has also been associated with decrements in bone health in frail older persons. Mechanistically, this is due to B-12's permissive effect on osteoblast proliferation. Folate was found to be protective against falls, such that for every 1 ng increase in serum concentrations, there was a 19% decrease in falls. These findings

point to higher levels of B12, zinc, folate, and vitamin D being associated with lower levels of physical frailty [98,99].

This review article is limited because it is a narrative review, focus on nutritional and frailty of elderly. We offer the information of nutrition support to prevent the transition of frailty into disability. But we did not focus on how to change the condition of "anorexia of aging". The mechanisms are not fully understood, Additional data from large-scale multi-center trials are still required.

Conclusion

Inadequate nutrient intake is frequent among elderly people and related to increasing dependence and care needs. An association between poor nutritional intake and the frailty syndrome was demonstrated in numerous recent studies. Not only energy and protein intake have been linked to frailty and frailty-related parameters. Particularly, the role of micronutrients with antioxidative capacity in the development of frailty has been highlighted in recent publications. Intake of micronutrients has found to be associated with frailty or related parameters of physical functioning, sometimes even independent from energy intake. Macro- as well as micronutrients may be regarded one of the key factors contributing to the development and aggravation of frailty. Particularly, uncovering the role of micronutrients in this context may lead an increased perception of the need to improve the quality of food eaten by elderly people-not just the quantity. Consequently, the goal will be raise general dietary intake of high-quality food provide both macronutrients and micronutrients.

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